REMARKS

In the Claims:

Claims 15-23 and 33-41 are pending in this case. Claim 24 has been canceled without prejudice as being drawn to a non-elected species. Claim 15 has been amended. Support for this amendment can be found throughout the specification, especially in Examples 6 and 12. New claims 33-41 have been added. Support for new claims 33-41 can be found throughout the specification, especially in Example 12.

Claim Rejections – 35 U.S.C. §112, First Paragraph, Written Description

Claim 15 (and Claims 16-19, 21and 22 which depend therefrom) remains rejected under 35 U.S.C. §112, first paragraph, on the grounds that the written description fails to describe the invention in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time of filing. The Examiner allows that the disclosed mode of delivery may be effective for delivery of a second sequence but is of the opinion that the Applicant has not shown possession of the second sequences recited in the claims. As pointed out in previous responses, the claims of the present application are not directed to any specific set of second sequences but rather are directed toward a novel mechanism for delivery of these sequences.

The Applicant wishes to direct the Examiner's attention to the existence of numerous issued U.S. Patents that have claims directed toward mechanisms for delivering nucleic acids or other active bioagents. See, for example, United States Patent No. 6,632,670, entitled "AAV vectors for gene therapy", issued October 14, 2003; United States Patent No. 6,436,708, entitled "Delivery system for gene therapy to the brain", issued August 20, 2002; United States Patent No. 6,147,278, entitled "Plant vectors", issued November 14, 2000; United States Patent No. 5,908,635 , entitled "Method for the liposomal delivery of nucleic acids", issued June 1, 1999;

United States Patent No. 6,228,393, entitled "Drug delivery via therapeutic hydrogels", issued May 8, 2001 ; United States Patent No. 6,544,782, entitled "pREM: a positive selection vector system for direct PCR cloning", issued April 8, 2003 ; United States Patent No. 6,399,383, entitled "Human papilloma virus vectors", issued June 4, 2002 , United States Patent No. 6,312,682, entitled "Retroviral vectors", issued November 6, 2001; and United States Patent No. 6,110,490 , entitled "Liposomal delivery system for biologically active agents", issued August 29, 2000. All of the foregoing have claims directed toward compositions and/or methods for delivering bioagents into the cells of organisms. These patents are not limited to specific agents but rather allow the use of a composition (i.e. plasmids, vectors, liposomes, hydrogels, etc) to introduce any number of agents that may find therapeutic use. Applicant requests that the instant application be afforded the same analysis and accordingly respectfully requests withdrawal of the outstanding rejection of Claims 15 (and Claims 16-19, 21and 22 which depend therefrom) under 35 U.S.C. §112, first paragraph.

Additionally, one of skill in the art reading the specification would have understood that that Applicant had possession of the present invention at the time of filing. The specification clearly sets forth numerous examples of possible insecticidal sequences that could be used in conjunction with a nucleic acid molecule encoding at least one capsid protein of an insect small RNA virus for delivery into an insect cell. For example, the specification sets forth that possible second sequence include various nucleotide sequences with insecticidal activity or which encode various toxins to an insect. Nucleotide sequences in the form of RNA or DNA which can be used include those of the HaSV genome or other insect viruses. Toxins which can be used advantageously include those which are active intracellularly and may also include neurotoxins with an appropriate transportation mechanism to reach the insect neurons. [Specification pages 19-20]

Additional examples of toxins disclosed in the specification that may be encoded by the second nucleic acid sequence include, *Bacillus thuringiensis* d-toxin, insect neurohormones, insecticidal compounds from wasp or scorpion venom or of heterologous origin, or factors

designed to attack and kill infected cells in such a way so as to cause pathogenesis in the infected tissue (for example, a ribozyme targeted against an essential cellular function). [Specification, page 24, lines 1-9] Furthermore, the specification sets forth that nucleic acid constructs may also be provided which include mechanisms for regulating pathogen expression (for example, mechanisms which restrict the expression of ribozymes to the insect cells) by tying for example, expression to abundant virus replication, production of minus-strand RNA or sub-genomic mRNA's so as to achieve a limited-spread system (such as control of replication). [Specification, page 24, lines 11-24]

Example 12 of the specification provides a detailed discussion of the types of nucleic acids and toxins encoded by the nucleic acids that may be used in the invention. The examples given provide a solid sampling of the possible toxins that may be used, but are not to taken as a complete listing.

Furthermore, the specification provides adequate guidance that one of skill in art would recognize that the invention could be used to deliver any number of other nucleic acids of interest into a cell in the gut of an insect for expression, or insecticidal function, therein.

For the foregoing reasons, the specification provides adequate description of the invention as recited in the claims such that one of skill in the art would recognize that the Applicant had possession of the invention at the time of filing the instant application.

Claim Rejections – 35 U.S.C. §112, First Paragraph, Enablement

Claims 15-19 and 21-23 are rejected under 35 U.S.C. §112, first paragraph, for lacking enablement. The Examiner finds the specification enabling for isolated nucleic acids comprising a first sequence encoding an insect RNA virus capsid protein and a second sequence that encodes an insecticidal protein. However, the Examiner asserts that the specification does not reasonably provide enablement for the claimed nucleic acids where the second sequence is a ribozyme,

antisense, or other insecticidal nucleic acid. The Examiner agrees that the claimed invention satisfies the problem of delivery and that the issue of toxicity of the second sequence is not relevant. However, the Examiner maintains his rejection based on the opinion that the specification provides no identification of, or guidance toward, antisense or ribozyme sequences that have insecticidal effects.

As set forth in the Written Description discussion above, the Applicant again asserts that exact identity of the second sequence is not necessary for the practice of the invention. One of skill in the art would be able to use the capsid protein of the insect small RNA virus to deliver the antisense or ribozyme sequence of choice. Thus, as with any plasmid vector or polymer delivery system, the exact identity of the agent to be delivered, in this case an antisense or ribozyme sequence, need not be determined until the invention is used by one of skill in the art for a particular application of insecticidal nucleic acid(see the list of issued United States Patents that claim compositions and/or methods for delivering unspecified bioagents provided above).

Furthermore, the Applicant asserts that the specification provides guidance so that one of skill in the art would understand that ribozymes and antisense nucleic acids could be used as a insecticidal second sequence. Specifically, on page 24, lines 4-9, the specification sets forth that ribozymes targeted against an essential cellular function are considered substances that are deleterious to insects. Additionally, on page 116, point 2, the specification discusses toxicity from RNA secondary structures and specifies that ribozymes and antisense nucleic acids are included as sequence structures useful in generating toxicity based on their secondary structure.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech Inc. v. Monoclonal Antibodies, Inc. 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463 221 USPQ 481, 489 (Fed. Cir. 1984). Applicant maintains

that this burden has been met and accordingly requests withdrawal of the outstanding enablement rejection under 35 U.S.C. §112, first paragraph.

Claim Rejections – 35 U.S.C. §103(a) – *Wilcox, et al.* in view of *Harley, et al.*

Claims 15, 16, and 19-23 remain rejected under 35 U.S.C. §103(a) as being anticipated by *Wilcox, et al.* in view of *Harley, et al.* Applicant respectfully disagrees with the rejection for the reasons below.

To establish a *prima facie* case of obviousness under 35 U.S.C.§103, the Examiner must demonstrate that, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. Further, the prior art must provide one of ordinary skill with a reasonable expectation of success. M.P.E.P. §2143.

Additionally, the prior art references must be enabling. "In order to render a claimed apparatus of method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989). Thus, the prior art references must allow one of skill to make and use the claimed nucleic acid constructs.

Wilcox, et al. teaches insecticidal fusion proteins expressed as polypeptide products of a hybrid gene comprising a cytoxic agent (*e.g.*, a ribosome inactivator such as ricin) and a bacterial insect gut cell recognition ("binding") protein which directs the cytotoxic agents to the host targets. *Harley, et al* merely relates to the identification of three viruses which infect *Helicoverpa armigera.*

The Examiner asserts that it would be obvious to use the capsid proteins of the CPV virus of *Harley* with the fusion proteins of *Wilcox* to arrive at the present invention. However, the references, when taken together, do not teach all aspects of the present invention.

Claim 15, as amended, recites an isolated nucleic acid molecule comprising a first sequence encoding at least one capsid protein of an insect small RNA virus and a second sequence which is insecticidal or which encodes an insecticidal protein toxin, wherein said capsid protein comprises an insect midgut cell binding domain. Neither Wilcox nor Harley teach or suggest a nucleic acid comprising a first sequence encoding at least one capsid protein wherein the capsid protein has an insect midgut cell binding domain. The Examiner states that one of skill in the art reading Harley would have a reasonable expectation that the virus disclosed therein targeted the insect gut. However, Harley does not teach that the virus disclosed has an insect midgut cell binding domain. The fact that one of the viruses, the CPV virus, was isolated from the midguts of *H. armigera* insects does not indicate that the virus necessarily targets the midgut. Harley provides no evidence that the CPV virus is not found in other areas of the infected insect. Additionally, Wilcox does not teach or suggest a virus that encodes a capsid protein comprising a insect midgut cell binding domain. Rather, Wilcox discloses the use of a specific bacterial gut targeting protein rather than a viral sequence to do the same. Since Harley provides only physical data on the nucleic acid isolated from the CPV virus it does not teach or suggest that (1) the CPV virus contains nucleic acid that encodes a capsid protein or (2) the CPV virus nucleic acid encodes a protein that has a midgut binding domain. As such, the cited prior art does not teach all of the elements of the invention.

Additionally, Harley does not enable one of skill in the art to make and use the claimed invention. Harley provides no guidance on how to identify or isolate a nucleic acid sequence from the CPV virus that would possibly be useful in the targeting a second nucleic acid sequence to an insect cell.

For the above-discussed reasons, the combination of Wilcox and Harley do not render the claimed invention obvious. Applicant respectfully requests withdrawal of the rejection.

Accordingly, the Applicant asserts that amended claim 15 (and claims 16 and 19-23 which depend therefrom) is not obvious over the cited prior art.

CONCLUSION

Applicants submit that the claims are now in condition for allowance. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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